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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/715,284
Filing Date: November 17, 2003
Appellant(s): AKHAVAN-TAFTI ET AL.

Richard Handley, Ph.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/1/2007 appealing from the Office action mailed 1/25/2007

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

Claims 1,2,4,5,8-12,22, 23, 27,28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Lough et al "Bead linkers for immobilizing nucleic acids to solid supports" 1999 US Patent No. 5,900,481.

Hughes "Application of polymer-bound phosphonium salts as traceless supports for solid phase synthesis" 1996 Tetrahedron Letters 37:7595-7598.

Bernard et al "Wittig reagents bound to cross-linked polystyrenes" 1983 JOC 48:326-332 1983.

Ching et al "Synthesis and preliminary DNA-binding studies of diimineplatinum(II) containing 3- or 4-pyridineboronic acid" vol. 2007 Royal Society of Chemistry Dalton Translations 2121-2126.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1,2,4,8,11 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Hughes** (1996 Tetrahedron Letters 37: 7595-7598) and **Lough et al** (US Patent 5900481).

Claim 1 is drawn to a solid phase for binding nucleic acids comprising:

a solid support portion comprising a matrix comprising at least one of silica, glass, insoluble synthetic polymers, or insoluble polysaccharides,

a nucleic acid binding portion for attracting and non-covalently and non-sequence specifically binding nucleic acids wherein the nucleic acid binding portion comprises at least one of a ternary sulfonium group, a quaternary ammonium, or a quaternary phosphonium group $PR_3^+ X^-$, and

a cleavable linker portion linking the nucleic acid binding portion to the solid support.

The *elected species* comprises a solid-support composed of silica, a hydrolytically cleavable linker and an aralkyl quaternary phosphonium salt nucleic acid binding moiety, as reflected in claims 2,4,8 and 11.

Hughes teaches throughout the publication and especially in scheme 2 and footnote 13, hydrolysis of an aralkyl quaternary phosphonium ylide (salt) from a solid matrix.

Hughes does not teach silica as the solid support, however. Furthermore, Hughes does not teach the support for binding of nucleic acids.

Lough et al teach throughout the publication, and especially column 3, lines 25-26 silica as a support for binding nucleic acids.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made, to employ the chemistry developed by Hughes with the nucleic acid binding silica beads of Lough et al.

One of ordinary skill in the art would have been motivated to make and use the chemistry of Hughes with the silica beads of Lough et al to take advantage of the chemical versatility afforded by orthogonal nucleic acid binding, as noted by Lough et al in column 5 lines 18-31.

One of ordinary skill could do so with a reasonable expectation of success since silica immobilized phosphonium salts are well known in the art.

(10) Response to Argument

Before addressing Appellant's arguments, the examiner submits that a few words are in order concerning the complete teachings of Lough et al and Hughes, which were not fully addressed in the Appeal Brief on p 4-5.

Lough et al

Lough et al teach, throughout the document and especially the abstract and figure 1 compositions comprising beads conjugated to a surface which are further conjugated to a nucleic acid. Notably, Lough et al teach *two* types of solid supports: bead and surface. Similarly, Lough et al teach *two* kinds of linkers based on, for instance : trityl groups, streptavidin/biotin binding; hydrophobic or ionic interactions as well as amide and disulfide bond formation (see column 5, lines 5-14; column 3, lines 40-45; column 4 line 59). In summary, the beaded composition according to Lough et al may be represented as: DNA-linker 1-Bead-linker 2-surface.

It is not clear to the examiner how Appellant has concluded that any the aforementioned linking chemistries require a known or selected nucleic acid sequence, as alleged on p 5 line 14-15 in the Appeal brief entered 10/1/2007, since each of trityl linkers, streptavidin/biotin binding, hydrophobic interaction, ionic interactions, amide bond formation and disulfide bond formation do *not* require a known or selected nucleic acid sequence for immobilization.

Each kind of linker according to Lough et al may be orthogonally cleavable and are thus quite versatile, allowing for cleavage of said nucleic acid from said bead or alternatively removal of said bead from said surface, such that each reaction is capable of being performed independently of one another. In other words, the nucleic acid may

be cleaved, whilst the bead remains immobilized on a surface *or* vice versa: the bead may be cleaved from surface, whilst the nucleic acid remains attached to the bead. (see column 5, lines 19-30).

The versatility of said DNA-linker 1-Bead-linker 2-surface compositions according to Lough et al is reflected in the large number of suitable applications including fluorescence, mass spectrometry and NMR spectroscopy, etc. (see column 5, lines 45-61 and further discussion below)

Hughes et al

Hughes et al teach throughout the document, and especially scheme 2, the use of immobilized phosphonium salts for traceless synthesis of various organic moieties via three pathways including (i) an intermolecular Wittig reaction (scheme 2 left), (ii) alkaline hydrolysis (scheme 2 middle) and (iii) an intramolecular Wittig reaction (scheme 2 right).

Appellant's Arguments

Appellant argues (i) not all elements are taught; (ii) a claim limitation has been improperly interpreted; (iii) a lack of a reasonable expectation of success; (iv) a lack of motivation to combine references.

Appellants arguments have been considered but are not persuasive for the following reasons.

(i) Specifically, Appellant argues, see Appeal Brief paragraph bridging pp 6-7, claim 1 and the claims dependent thereon require both "a nucleic acid binding portion for attracting and non-covalently and non-sequence specifically binding nucleic acids

wherein the nucleic acid binding portion comprises at least one of a ternary sulfonium group, a quaternary ammonium,or a quaternary phosphonium group $PR_3^+ X^-$" **and** "a cleavable linker portion linking the nucleic acid binding portion to the solid support."

In so far as the nucleic acid binding portion is concerned, Appellant admits on p 14 line 3 of the Appeal Brief, "It is telling that reversible immobilization or nucleic acids on positively charged surfaces was well known in the art before the time of Lough's inventions..." The examiner submits that the immobilized phosphonium salts of Hughes et al fall into the category of a positively charged surface providing the nucleic acid binding portion set forth in claim 1.

In so far as the cleavable linker portion is concerned, the present specification in paragraph 0052 of the published application defines cleavable linkers as:

> The **cleavable linker portion** is preferably an organic group selected from straight chains, branched chains and **rings** and comprises from 1 to 100 atoms and more preferably from **1 to about 50 atoms**. The atoms are preferably selected from **C**, H, B, N, O, S, Si, P, halogens and alkali metals. An **exemplary linker group is a hydrolytically cleavable group** which is **cleaved by hydrolysis**. Carboxylic esters and anhydrides, thioesters, carbonate esters, thiocarbonate esters, urethanes, imides, sulfonamides, and sulfonimides are representative as are sulfonate esters. Another exemplary class of linker groups are those groups which undergo reductive cleavage. **One representative group is an organic group containing a disulfide (S--S) bond which is cleaved by thiols such as ethanethiol, mercaptoethanol, and DTT.**

Emphasis added.

The examiner submits, for example, the Trityl linker of Lough et al comprises rings, is from 1 to 50 Carbon atoms and is hydrolytically cleavable, thus falls squarely into the category of cleavable linker portion, as defined above.

Furthermore, the examiner submits that the teachings of Lough et al and Hughes may be put together in many ways which read on the claimed subject matter. For example, one of skill in the art might construct DNA^- ::: RP^+Ph_2-Optional Spacer-Trt-Bead, with RP^+Ph_2- from Hughes. Note that negatively charged DNA is adsorbed on the positively charged bead by electrostatic interaction (:::), as described above.

Focusing on the chemistry on the bead, the examiner submits that the above construct when submitted to acid hydrolysis will release DNA^- and RP^+Ph_2-Optional Spacer into solution whereas Trityl remains on the support as HO-Trt-Bead, which is analogous to figure 3 and column 5, lines 5-14 of Lough et al. Alternatively, when the same construct is submitted to alkaline hydrolysis, negatively charged DNA^- will desorb from the thus prepared neutral phosphine oxide support ($O=PPh_2$-Optional Spacer-Trt-Bead), in accordance with the middle pathway of Hughes scheme 2. The examiner submits that both mechanisms read on claims 1,2,4,8 and 11. Please note that Hughes et al is silent with regard to the fate Phosphorous atom, which is discussed in greater detail in sections (ii and iii) below.

In conclusion, the immobilized phosphonium salt of Hughes et al provides a nucleic acid binding portion for attracting and non-covalently and non-sequence specifically binding nucleic acids wherein the nucleic acid binding portion comprises a quaternary phosphonium group $PR_3^+ X^-$, such as set forth in claim 1. In

Trityl, Lough et al provide a cleavable linker portion linking said phosphonium salt of Hughes to a solid support (bead) in accordance with claim 1.

As an aside it is noted, the present specification in paragraph 0031 of the published application defines solid phase materials as:

> Solid phase material--a material having a surface to which can attract nucleic acid molecules. Materials **can be in the form** of microparticles, fibers, beads, membranes, and other supports such as test tubes and microwells.
>
> Emphasis added.

And, in this regard, it is noted that a *surface* type of as a solid support, such as suggested by Lough et al *is not excluded* in the above definition. Thus, the DNA˙ ::: $RP^{+}Ph_2$-Optional Spacer-Trt-Bead construct may be further immobilized on a surface through a disulfide linker, cleavable by thiolysis, as described by Lough et al in column 5, lines 24-25, which reads on claims 1,2,4,8.

(ii) Appellant specifically argues, see Appeal Brief p 8-11 that the examiner has interpreted the term "cleavable" to refer to only release of DNA from the solid support which is inconsistent with the specification as filed in that the description and the worked examples which provide for cleavage of the onium salt in concert with DNA release.

In response to appellant's argument that the references fail to show certain features of appellant's invention, it is noted that the features upon which appellant relies (i.e., cleavage of the onium salt) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are

not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Here, alkaline hydrolysis under Wittig reaction conditions (NaOMe, MeOH in accordance with conditions a and d in Scheme 2 of Hughes) the examiner submits, generates a neutral phosphine oxide species on the support, which is supported by table IV of Bernard et al 1983 JOC 48:326-332 1983. Appellant asserts on p 10 lines 19-21 that examiner has not provided evidence on the record concerning generation of phosphine oxides under alkaline Wittig reaction conditions, it is noted, however Bernard et al was mentioned in the final office action mailed 1/25/2007 on p 3, last paragraph.

Table IV of Bernard et al concerns recycling of the phosphine oxide supports back to phosphonium salt immobilized polymers. See also Bernard et al, last line of the abstract. Notably, said phosphonium salt immobilized polymer of Bernard et al are the same as that of Hughes (see citation 11 to Ford on p 7596 line 7 of Hughes).

Regardless, assuming arguendo that the fate of the Phosphorous atom under alkaline Witting reaction conditions does not provide a neutral phosphine oxide species and thus DNA is not released from the support, as alleged by Appellant, it is noted *acid* hydrolysis at the Trityl linker according to Lough et al provides for release of phosphorous with concomitant with DNA release, as described above.

(iii) Appellant specifically argues, see Appeal Brief p 12 that the predominant resonance structure of phosphine oxide generated under alkaline cleavage conditions bears a full negative charge on the oxygen atom and a corresponding full positive

charge on the phosphorous, leading to a net zero charge. The examiner submits that that said zero charged species represents a type of Zwitterion.

Appellant has invited (see Appeal Brief p 12 line 3) the examiner to provide evidence that zwitterions do not interact with DNA, which is set forth herein by Ching et al (vol. 2007 Royal Society of Chemistry Dalton Translations 2121-2126) who state on p 2124 left column lines 28-32:

> ...the boronic acid groups exist predominately in their anionic boronate form which means [compounds] 3–6 are **zwitterionic** in solution and thus **electrostatic interactions with DNA are unfavoured owing to their overall neutral charge**...

Emphasis added. Appellant admits, see Appeal Brief p 12, lines 11-12, "the effect of the strong polarization charge [of phosphine oxide] on nucleic acid binding and release is unknown." The examiner submits accordingly, Zwitterions, according to Ching et al have unfavorable interactions with DNA, thus alkaline treatment of phosphonium salts leading to Zwitterionic phosphine oxides, such as prepared under alkaline Wittig reaction conditions would cleave DNA from a support due to unfavorable interactions.

Furthermore according to In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990): "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." Here, appellant has not presented evidence on the record showing DNA as having affinity for phosphine oxides and the PTO has sound basis to believe Zwitterions such as immobilized phosphine oxides would desorb DNA due to unfavorable interactions, according to Ching et al.

Again, assuming arguendo that the fate of the Phosphorous atom under alkaline cleavage conditions does not afford DNA cleavage from the support, as alleged by Appellant, it is noted the acid hydrolysis at the Trityl linker according to Lough et al disconnects phosphorous from the support with concomitant with DNA release.

(iv) Appellant specifically argues, see Appeal Brief p 13-14 there is a lack of motivation to combine references because, by promoting non-specific binding, the phosphonium salt of Hughes would thwart the ability to perform hybridization experiments such as Sequencing By Hybridization (SBH) advocated by Lough et al in the paragraph bridging of column 5 and 6.

In this regard, the examiner submits the beaded surfaces or Lough et al have applications beyond SBH. In particular, in the same passage, Lough et al suggest the invention provides for combinatorial libraries of immobilized nucleic acids. The examiner submits combinatorial libraries of immobilized nucleic acids would necessarily *require* non-specific binding, in order to bind all members of a nucleotide library.

Moreover, Lough et al mention the value of kits for immobilizing nucleic acids in column 6, lines 4-10, including a conjugation means. The examiner submits that said conjuagtion means would necessarily need to be non specific to be useful.

The examiner therefore submits, to prepare, for instance, a universal kit for immobilizing combinatorial libraries of nucleic acids, would require non-sequence specificity and one of skill in art at the time the invention was made would have been motivated to use the immobilized phosphonium salt of Hughes as linker 1 in the DNA-linker 1-Bead-linker 2-surface composition according to Lough et al.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

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